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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/830,779	11/30/2001	Kenneth Chien	6627-PA9025	3690
27111	7590	01/20/2004	EXAMINER	
BROWN, MARTIN, HALLER & MCCLAIN LLP 1660 UNION STREET SAN DIEGO, CA 92101-2926			DUFFY, PATRICIA ANN	
		ART UNIT	PAPER NUMBER	
		1645	13	

DATE MAILED: 01/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/830,779	CHIEN ET AL.
	Examiner	Art Unit
	Patricia A. Duffy	1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.

- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.

- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.

- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 05 September 2003.

2a) This action is FINAL. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 1, 4, 12, 16, 19, 20, 22 and 23 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) Claim(s) 1, 4, 12, 16, 19, 20, 22 and 23 is/are rejected.

7) Claim(s) _____ is/are objected to.

8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some * c) None of:

1. Certified copies of the priority documents have been received.

2. Certified copies of the priority documents have been received in Application No. _____.

3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) The translation of the foreign language provisional application has been received.

14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) <input type="checkbox"/> Notice of References Cited (PTO-892)	4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____.
2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)
3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>11</u> .	6) <input type="checkbox"/> Other: _____.

RESPONSE TO AMENDMENT

The amendment filed 9-5-03 has been entered into the record. Claims 2, 3, 5-11, 13-15, 17 and 18 have been cancelled. Claims 1, 4, 12, 16, 19, 20, 22 and 23 are pending and under examination.

The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

Information Disclosure Statement

The information disclosure statement filed 9-5-03 has been considered. An initiailled copy is enclosed.

Rejections Maintained

Priority

Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. However, the provisional application upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for claim of this application for the treatment of heart failure or enhancement of cardiac contractility by addition of an exogenous dominant negative penetratin peptide functionally attached to a dominant negative phospholamban protein/mutant or truncated version of a phospholamban protein.

Claims 4, 12, 14, 16, and 18-23 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is maintained for reasons made of record and reasons set forth herein.

The claims are drawn to methods of inducing PLB deficiency wherein an exogenous dominant negative PLB protein functionally attached to a penetratin peptide induces phospholamban deficiency or method of treatment of heart failure comprising enhancement of cardiac contractility wherein the exogenous dominant negative PLB protein is used to inhibit interaction between PLB and sarcoplasmic reticulum calcium ATPase (SERCA2a). Applicants teach at page 2, second full paragraph that activity of the cardiac sarcoplasmic reticulum Calcium ATPase (SERCA2a) is regulated by phospholamban (PLB), a 52 amino acid muscle-specific sarcoplasmic reticulum phosphoprotein. The specification also teaches that PLB exists primarily in a pentameric form and that when subjected to high temperature, dissociates into five equivalent monomers (page 3, lines 3-6). It is noted that the sarcoplasmic reticulum is a organelle that lies completely inside muscle cells and surrounds myofibrils. The sarcoplasmic reticulum is surrounded by the cell cytosol and the sarcoplasmic reticulum is surrounded by and separate from the plasma membrane (see pages 825-827 of Darnell et al, Molecular Cell Biology, Scientific American Books, Inc. 1986). Applicants acknowledge at page 5, lines 7-10, that the internalization of exogenous molecules to enhance cardiac contractility by live myocytes remains an unresolved issue. The specification is devoid of any teachings that indicate that this problem has been actively solved, either *in vitro* or *in vivo*. The specification further teaches that the non-phosphorylated PLB inhibits SERCA2a (page 11, lines 16-20). While the specification teaches gene-mediated ablation of endogenous PLB in a double-knockout mouse enhances cardiac contractility, there is no teaching of how to apply, administer a exogenous dominant negative PLB protein, PLB mutant or truncated PLB in order to induce PLB deficiency as claimed. Further, the penetratin-PLB mutants described and tested at pages 30-31 of the instant specification did not function to enhance cardiac contractility as measured by contacting isolated cardiomyocytes with the dominant negative penetratin-PLB mutants. The specification teachs "While their appeared to be a trend towards a larger, faster contraction in the myocyte, T-test analysis not identify any statistical

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difference due to the high variability of the data." (page 31, lines 9-11). Since, the claimed dominant negative penetratin-PLB peptide mutants do not provide for enhanced cardiac contractility *in vitro*, the claimed dominant negative penetratin-PLB-mutants can not provide for a difference *in vivo*. The specification does not teach that the claimed penetratin-PLB polypeptides when applied exogenously either *in vitro* or *in vivo*: (a) do in fact enter the cardiac myocyte and (b) enter in sufficient quantities to treat heart disease or enhance cardiac contractility as claimed. In fact, the specification specifically teaches that no statically significant difference was observed *in vitro*. Since the function of penetratin to translocates heterologous peptides across a cell membrane is not specific to cardiomyocytes, mere delivery of the dominant negative polypeptide drug peptide by conventional routes would lead to translocation across any available cell membrane. It is noted that unlike the controlled situation *in vitro*, *in vivo* cells possessing membranes outnumber cardiomyocytes by the millions. Even if one were to demonstrate post filing that the claimed exogenous PLB proteins entered cardiac myocytes *in vitro*, the *in vivo* situation is still highly complex. As previously set forth in the specification, PLB is not specific to cardiac myocytes (cardiac muscle cells), but to myocytes (i.e. muscle cells) in general and as such, if taken up by cardiac muscle cells would also more likely than not, be taken up by other muscle cells. It is noted that cardiac muscle mass is a small component of the total muscle mass of an average adult (skeletal muscle + smooth muscle + cardiac muscle). In a non-specific means of uptake all of even just the muscle would take up the exogenous dominant negative penetratin PLB protein/mutant/truncated form and as such it is not clear from the specification as filed whether there can be sufficient administered in any manner, to achieve the goals of the claims (i.e. induction of phospholamban deficiency or enhancement of cardiac contractility). Unlike gene-mediated transfection of cells (i.e. the non-elected invention), there is no constant production of the protein in the cells and therefore it is not readily apparent that sufficient protein can be administered *in vivo* or *in vitro* to provide the functionality as claimed. The courts have held "... in cases

involving predictable factors, such as mechanical or electrical elements, a single embodiment provide broad enablement in the sense that once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved." (*In re Fisher* 166 USPQ 18 (CCPA)). The state of the art at the time of filing was unpredictable and remained unpredictable post filing. Inasmuch as, the specification teaches that no statically significant increase in myocyte contractility was observed *in vitro*, one skilled in the art would no expect that the it would work *in vivo* as claimed.

Applicants arguments have been carefully considered but are not persuasive. Applicants argue that the art teaches that that the translocation of proteins of a size comparable to a PLB-penetratin peptide fusion is taught at a relatively low concentration of peptide ad cites Derossi et al (J. Biol. Chem. 269:10444-50, 1994). This is not persuasive because it demonstrates that the pANTp unaltered homoeodomain of about 60 amino acids long translocates and does not address the issue of the movement of a fusion polypeptide. Additionally, the claims are not structurally and functionally limited to this structure. Even if they were, there is still no evidence of record that establishes that the claimed dominant negative penetratin-PLB mutants effectively penetrate the cell *in vitro* or *in vivo*. Further, Derossi et al emphasize that the translocation is not receptor specific and functions in any cell membrane and therefore no delivery means is described in the specification that gets around this issue of non-specific uptake by other cells. Applicants argue that Frankel et al (U.S. Patent 5,652,122) teach that a peptide of 123 aa acids in length fused to a penetratin peptide from TAT is transported in sufficient quantities to exert a physiological effect. This is not persuasive, it represents *in vitro* results that do not translate to specific administration to cardiac myocytes *in vivo*. This is also again not persuasive, because in contrast to Frankel et al, Applicants own specification indicates

that no statistically significant effect was observed *in vitro*. A heart is a collection of myocytes. Since, the average of *in vitro* results roughly represents a collection of myocytes *in vivo*, there is substantial reason to doubt that the claimed peptides are effective *in vivo* ... even if one could get a sufficient quantity to the heart (a point that the examiner does not concede). Frankel et al does not address tissue specific delivery *in vivo*. Applicants argue that the translocation of a penetratin peptide across a membrane is believed to involve multimerization of the homeodomain and therefore the effective size is the transported protein is larger than the penetratin peptide-PLB fusion. This is again not persuasive because it raises the issue of the ability of the multimer to physiologically function internal to the cell. Additionally, Applicants indicate that the penetratin peptide-PLB is a fusion, however the claims are not so limited. Applicants submit that the mechanism by which the peptide enters the cell need not be known for the claim to be enabled and that those skilled in the art were knowledgeable about the use of penetratin peptides and would have been able to design peptides that would be delivered to the cell. This is not persuasive, it is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of the invention in order to constitute adequate enablement." *Genetech Inc. v. Novo Nordisk A/S* 42USPQ2d 1001. Applicants assert that the PLB-penetratin peptide would be inserted into the membrane by the same mechanism as endogenous PLB. This is not persuasive, there is no evidence that the claimed penetratin functionally linked to dominant negative PLB peptide has this ability. The mechanisms of insertion of PLB into the sarcoplasmic reticulum is as stated by Fujii et, remains unknown. Because the mechanism is unknown and it is clear that dominant negative PLB proteins of the art function differently (see art of record), the conclusion lacks any evidentiary support. Applicants argue that the examiner states that specific delivery to cardiac myocytes is concern and submit that a number of devices for delivery of compounds to the pericardium were well known at the time of filing of the instant invention. This is not persuasive, delivery to the pericardium is not set forth in the claims

and is not contemplated by the specification as filed. The "delivery to cardiac tissue" encompasses, intramuscular, intravenous, sublingual, oral etc. The claims are not limited to the direct delivery means of the recited patents and are site-specific delivery. The claims do not recite such site-specific delivery and do not contemplate these site-specific delivery mechanisms as part of the written description. "Delivery" is not so limited. It is noted that enablement must be established in the specification at the time of filing and is to be commensurate in scope with the stated claimed. *In re Hogan and Banks*, 194 USPQ 527 (1977). Applicants further argue that Example 5 provides suggestive data. This is not persuasive, as previously set forth, the specification explicitly teaches "While their appeared to be a trend towards a larger, faster contraction in the myocyte, T-test analysis not identify any statistical difference due to the high variability of the data." (page 31, lines 9-11). The *in vitro* data does not support the *in vivo* physiological functioning of the claimed penetratin-dominant negative PLB peptides, truncations etc. Even if one of skill in the art delivered it to the pericardium, the lack of any significant statistical different provides reason to doubt the assertion of Applicants that such would work. Applicants assertions that the claimed invention would work *in vivo*, in view of the lack of statistical difference reported by Applicants *in vitro*, is not persuasive because it lacks evidentiary support. Further, delivery is not limited to the pericardium and is not contemplated by the written description as filed.

The rejection is maintained.

Claims 4, 12, 14, 16, and 18-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The rejection is maintained. The claims still do not recite an active method step. The past tense of "d livered" is not viewed as an active method step. This issue may be resolved by amending the claim to recit "A m thod for treatment of heart failure

comprising delivering to cardiac tissue an exogenous dominant negative phospholamban (PLB) protein functionally attached to a penetratin peptide in an amount sufficient to induce phospholamban deficiency.

New Rejections Based on Amendment

Claims 1, 4, 12, 16, 19, 20, 22 and 23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The claim recite an exogenous "dominant negative" phospholamban (PLB) protein functionally attached to a penetratin peptide". The specification as originally filed fails to describe any polypeptide as "dominant negative". This issue is best resolved by Applicants pointing to the specification by page and line number were "dominant negative" polypeptides are described.

Additionally, while the specification teaches the subgenus of covalent linkage of the penetrating peptide to the PLB by means of covalent peptide linkages, the generic term "functional linked" encompasses any means of functionally linking the recited members. These means include, for example, non-covalent and chemical linkages. These functional linkages were not conceived in the specification as filed. Therefore, the specification as originally filed fails to provide written description support for conception of the genus of "functional linkage" as is now claimed and as such introduce new concepts. *In re East and Harmon (CCPA) 181 USPQ 716 (May 9, 1994).*

Claims 1, 4, 12, 16, 19, 20, 22 and 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claim recited an exogenous "dominant negative" phospholamban (PLB) protein functionally attached to a penetratin peptide". There is no such thing as a dominant negative protein and this is not defined in the specification. Dominant negative is discussed as a phenotypic effect upon a cell and a relative term to some normal situation. The term is not described in terms of a polypeptide by the phenotypic effect exerted by the administered polypeptide relative to a polypeptide that is not set forth in the claims. As such, the meaning of dominant negative as it relates to a particular polypeptide is unclear.

Applicants statements in regard to this issue are not persuasive. Dominant negative is in fact discussed in relation to the specific phenotypic activity of the administered mutant PLB. The claims do not set forth this concept. The specification does not define a dominant negative PLB and is only discussed in relation to the specific phenotypic effect in a cell and not the protein per se. As such, the use of the term "dominant negative PLB protein functionally attached to a penetratin peptide" is *prima facie* indefinite. Applicants response indicates that the term should be interpreted by means of the art, but on the other hand are not in fact limited by the teachings of the art with respect to that which is described as a dominant negative effect. This is not persuasive, because one can not rely upon an art definition of a term and then indicate that the subject matter is not limited by this art definition and recite an interpretation of the term that is not specifically supported by the specification as originally filed and is completely different than that of the art. The term is *prima facie* indefinite, it is not in fact defined by the art (i.e. dominant negative is used relative to a phenotypic effect on a cell and not the polypeptide per se), the specification as filed does not define this term, and Applicant argues that it

means something different than the art and is not limited by the art's description of the phenotypic effect of such.

Status of Claims

All claims stand rejected.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy whose telephone number is 703-305-7555 or 571-272-0855 after January 27, 2004. The examiner can normally be reached on M-F 6:30 pm - 3:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Smith Lynette can be reached on 703-308-3909. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Patricia A. Duffy
Patricia A. Duffy

Primary Examiner

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